



Universiteit
Leiden
The Netherlands

ANCA-associated glomerulonephritis : insights into etiology, pathogenesis, and prognosis

Lind van Wijngaarden, R.A.F. de

Citation

Lind van Wijngaarden, R. A. F. de. (2009, March 12). *ANCA-associated glomerulonephritis : insights into etiology, pathogenesis, and prognosis*. Retrieved from <https://hdl.handle.net/1887/13612>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/13612>

Note: To cite this publication please use the final published version (if applicable).



They say that time changes things,
but you actually have to change them yourself.
Andy Warhol





Chapter 3

Chances of renal recovery for dialysis-dependent ANCA- associated glomerulonephritis

Robert A.F. de Lind van Wijngaarden

Herbert A. Hauer

Ron Wolterbeek

David R.W. Jayne

Gill Gaskin

Charles D. Pusey

Niels Rasmussen

Laure-Hélène Noël

Franco Ferrario

Rüdiger Waldherr

E. Christiaan Hagen

Jan A. Bruijn

Ingeborg M. Bajema

for the European Vasculitis Study Group (EUVAS)

Published in *J Am Soc Nephrol* 2007 Jul;18(7):2189-97

Abstract

In patients with anti-neutrophil cytoplasm autoantibody (ANCA)-associated glomerulonephritis who are on dialysis at time of diagnosis, renal function is sometimes insufficiently restored by immunosuppressive treatment, which often coincides with potentially lethal adverse effects. We investigated the clinical and histological variables that determine the chances of dialysis independency, dialysis dependency, or death after 12 months in these patients.

Sixty-nine patients with ANCA-associated glomerulonephritis who were dialysis dependent at diagnosis received uniform, standard immunosuppressive therapy plus either intravenous methyl prednisolone or plasma exchange. Eleven clinical and histological variables were assessed. Univariate and binary logistic regression analyses were performed.

Predictive parameters were entered into a two-step binary logistic regression analysis to differentiate among the outcomes of dialysis independency, dialysis dependency, or death. The point at which the chance of therapy-related death exceeded the chance of dialysis independency was determined. The chance of recovery exceeded the chance of dying in most cases.

Intravenous methyl prednisolone as adjunctive therapy plus less than 18% normal glomeruli and severe tubular atrophy increased the chance of therapy-related death over the chance of dialysis independency. Plasma exchange treatment plus severe tubular atrophy and less than 2% normal glomeruli increased the chance of therapy-related death over that of dialysis independency.

Even with ominous histological findings, the chance of renal recovery exceeds the chance of therapy-related death if these patients are treated with plasma exchange as adjunctive therapy.

Introduction

In antineutrophil cytoplasm autoantibody (ANCA)-associated vasculitides, such as microscopic polyangiitis, Wegener's granulomatosis, and renal-limited vasculitis, a characteristic clinical feature is rapidly progressive deterioration of renal function. This deterioration may result in end-stage renal failure or death¹, especially when patients are dialysis dependent at diagnosis²⁻⁵, or have high initial serum creatinine levels^{6,7}. Histopathologically, pauci-immune crescentic glomerulonephritis appears, with variable amounts of extracapillary proliferation, fibrinoid necrosis, and glomerulosclerosis in the renal biopsy⁸. Patients with ANCA-associated glomerulonephritis are treated with immunosuppressive drugs, which are effective because they increase survival dramatically and induce complete remission in the majority of ANCA-associated vasculitis patients⁹⁻¹⁴. However, in approximately 10 to 15 percent of patients, renal function is inadequately restored⁹⁻¹⁴, most often in patients who have severe renal dysfunction at presentation^{2,5-7,10,14-18}. If immunosuppressive therapy fails, continuing dialysis is their only option. In the meantime, these patients have been exposed to the potentially lethal adverse effects of these drugs, such as infections^{9,19,20}.

The physician has to outweigh the chance of immunosuppressive treatment leading to renal recovery against the chance of severe adverse effects. It is a clinical challenge to distinguish at onset those patients who will benefit from immunosuppressive therapy and those who will not. If at disease onset patients could be identified who will not benefit from immunosuppressive therapy, these patients could be protected from the potentially lethal adverse effects of this therapy. Of course, extrarenal disease manifestations may justify immunosuppressive treatment, irrespective of renal involvement.

Previously, we reported on parameters that determine outcome in patients with ANCA-associated vasculitis with severe renal involvement defined as a serum creatinine level higher than 500 $\mu\text{mol/L}$ at diagnosis²¹. In the present study, we focused exclusively on those patients with ANCA-associated glomerulonephritis who were on dialysis at the time of diagnosis, investigating whether the hazards of immunosuppressive treatment in these patients outweigh the expectations on recovery. Several reports have found that renal function over time is worse if patients are already dialysis dependent at diagnosis^{2,5-7,10,14-18}, but dialysis-dependent patients with ANCA-associated glomerulonephritis have not been prospectively studied. The patients were a subgroup of the MEPEX trial, conducted by the European Vasculitis Study

(EUVAS) group.

The aim of the current study was to estimate at one year after diagnosis the chances of a dialysis-dependent patient having achieved renal recovery versus the chances of this patient still being on dialysis or of having died. We evaluated the characteristics of patients who died of therapy-related causes and those who died of causes not attributable to therapy. Moreover, we report on the clinical and histological parameters influencing outcome in patients who were dialysis dependent at presentation and analyze at what point the chance of therapy-related death exceeds the chance of dialysis independency.

Methods

Patients

Within the framework of the EUVAS, 29 hospitals in 11 European countries enrolled patients in the MEPEX trial, a randomized trial evaluating adjunctive therapy for severe glomerulonephritis in ANCA-associated systemic vasculitis ²². In the present study, patients were included from this trial who were dialysis dependent at entry. The local ethics committees approved the study, and all patients gave written informed consent for participation. Inclusion and exclusion criteria for MEPEX are described extensively elsewhere ^{21,22}. All patients followed a standard treatment regimen, which consisted of oral corticosteroids, started at 1.0 mg/kg daily and tapered down within the first six months, and 2.5 mg/kg cyclophosphamide daily, which at three months was replaced by the less-toxic azathioprine. For adjunctive therapy, patients were randomized to either receive intravenous methyl prednisolone or undergo plasma exchanges. Those patients who were randomized to receive intravenous methyl prednisolone were administered 1000 mg three times daily for three consecutive days, starting directly after diagnosis. The patients in the plasma exchange limb received seven plasma exchanges of 60 mL/kg during the first 14 days after diagnosis. Patients were only included in this analysis if they were on dialysis at diagnosis and if both histological data, obtained from renal biopsy at the time of study entry, and clinical data were available.

Disease definitions were adapted from the 1992 Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis ²³ and a previous European Union Study ²⁴. They were distinguished by criteria previously published and as such determined by local physicians ²².

Clinical outcome variables and their clinical and histological candidate predictors

In this study, clinical outcome variables were dialysis dependency and dialysis independency at 12 months, and death.

Because the number of variables was high and the number of cases relatively low in this study, inclusion of all variables in the regression analysis would not have been statistically relevant^{21,25}. To prevent "over-fitting", only the most promising variables were selected as candidate predictors of renal outcome on the basis of earlier findings^{17,21,25,26}. Eleven clinical and histological variables were examined. Age and type of adjunctive treatment (intravenous methyl prednisolone or plasma exchange) were candidates for clinical predictors of renal outcome.

Paraffin sections of renal biopsies were stained with silver, periodic acid-Schiff, and hematoxylin and eosin. These sections were reviewed by two of five participating pathologists (LHN, FF, RW, JAB, IMB). Both pathologists scored the biopsies separately and according to a previously standardized protocol for scoring renal biopsies of patients with ANCA-associated vasculitis^{27,28}. They were blinded to patient data and the scores of the other observer. Briefly, each glomerulus had to be scored separately for the presence of fibrinoid necrosis, crescents (cellular/fibrous and segmental/circumferential), and glomerulosclerosis. The presence of glomerular lesions was calculated as the percentage of the total number of glomeruli in a biopsy. Interstitial, tubular, and vascular lesions were scored dichotomously or semi-quantitatively. Discrepancies between the observers were resolved by conference during central reviews, achieving consensus for each biopsy.

Statistics

The computer program used to perform statistical analyses was the SPSS 10.0 standard version for Windows (SPSS, Inc., Chicago, IL, USA). For each test the statistical methods used are outlined in the next paragraphs.

Univariate analysis and logistic regression analysis, distinguishing between two outcome variables

Univariate correlation tests were performed to determine which of the 11 variables distinguished between two outcome variables, namely dialysis at one year versus death, dialysis independency at one year versus death, and dialysis independency versus dialysis dependency at one year. Quantitative

variables were correlated using Pearson's correlation test; for correlation with dichotomous or categorical variables, Phi-values were used. Each variable that showed a correlation with a P value of 0.10 or lower was entered into a binary logistic regression model as a potential predictor. This approach led to three formulas expressing the histological and clinical parameters that were predictive of differences between dialysis at one year and death, dialysis independency at one year and death, and dialysis independency and dialysis dependency at one year. Parameters that were shown to be predictors in any of the three formulas were used to construct the formulas of the two-step binary logistic regression analysis.

The two-step binary logistic regression analysis

Consequently, to calculate the chance on a certain outcome for each patient, a two-step binary logistic regression analysis was performed, mimicking a multinomial logistic regression model but providing more insight into the construction of the predictive models. In each step, a binary logistic regression model reflects the chance of a previously defined outcome. The first model differentiated between recovery -i.e., dialysis independency after 12 months- and unfavorable outcome: either dialysis dependency or death after 12 months. The second model distinguished between dialysis dependency and death after 12 months. These models are visualized in Figure 1. All parameters predictive in one of the binary logistic regression models that differentiated between two outcomes, as described above, were entered into and forced to stay in the two binary logistic regression models of the two-step analysis. With the help of these models, the chances of a certain outcome could be calculated for each patient (Figure 1).

Sensitivity values and predictive values for the outcomes were identified by creating classification tables. Chances of different outcomes for the phenotypically best and worst cases for this patient cohort were calculated to determine the range of chances of a certain outcome.

Comparing the chance of therapy-related death with the chance of recovery

We determined how many patients died how long after disease onset and from what cause. Patients who had died because of infection or sepsis were considered to have died of therapy-related causes. By setting out the values of parameters determining the chances of therapy-related death and dialysis independency, the point could be estimated at which the chance of therapy-related death exceeded the chance of recovery (i.e., dialysis independency).

Results

Patients

Of 69 dialysis dependent patients who entered the MEPEX trial, clinical and histological data were available. The number of glomeruli in the renal biopsies ranged from 2 to 49 with an average of 13.3 glomeruli per cross-section. Five patients had less than 6 glomeruli in their renal biopsy. Thirty-four of these patients were treated with intravenous methyl prednisolone and 35 with plasma exchange as adjunct to standard therapy. After 12 months, 30 (43%) had restored renal function and were no longer on dialysis, 22 (32%) were on dialysis, and 17 (25%) had died. Clinical characteristics are given in Table 1.

Table 1. Clinical characteristics for the whole group and for the different outcome groups

	Whole group	Dialysis independent	On dialysis	Dead
No. of patients	69	30	22	17
Age (range)[yr]	64.2 (26.8-78.4)	62.7 (28.4-76.4)	63.6 (26.8-78.4)	67.9 (56.6-78.2)
Gender (male/female)	42 / 27	16 / 14	17 / 5	9 / 8
Diagnosis (WG/MPA/RLV)	19 / 42 / 8	12 / 15 / 3	4 / 16 / 2	3 / 11 / 3
GFR ₁₂ (mL/min)* [mean ± SD]	31 ± 13	31 ± 13	-	-
Proteinuria (mg/24h) [mean ± SD]	31 ± 5	31 ± 5	31 ± 4	30 ± 6
Adjunctive treatment (IVMeP/PE)# [%]	49 / 51	11 / 19	16 / 6	7 / 10
Normal glomeruli [mean ± SD]	12 ± 17	14 ± 14	6 ± 8	17 ± 26
Fibrinoid necrosis [mean ± SD]	23 ± 23	25 ± 23	17 ± 23	27 ± 25
Segmental crescents [mean ± SD]	14 ± 15	16 ± 17	11 ± 13	13 ± 14
Fibrous crescents [mean ± SD]	7 ± 9	6 ± 11	8 ± 9	6 ± 8
Glomerulosclerosis [mean ± SD]	28 ± 24	23 ± 25	37 ± 25	23 ± 16
Interstitial infiltrates (-/+ /++ /+++)	0 / 22 / 34 / 13	0 / 8 / 18 / 4	0 / 10 / 8 / 4	0 / 3 / 9 / 5
Tubular atrophy (-/+ /++)	12 / 39 / 18	7 / 17 / 6	1 / 12 / 9	4 / 9 / 4
Intra-epithelial infiltrates (-/+)	12 / 57	8 / 22	1 / 21	3 / 14
Arteriosclerosis (-/+)**	19 / 43	12 / 12	4 / 17	3 / 14

* of patients who were dialysis independent at 12 months. # IVMeP = intravenous methyl prednisolone, PE = plasma exchange. ** In the biopsies of seven patients no arteries were detected.

Univariate analysis and logistic regression analysis, distinguishing between two outcome parameters

All of the 11 candidate parameters that distinguished between two outcomes with a $P < 0.10$ were entered into a regression model as candidate predictors. Since there were three pairs of two outcome parameters, this resulted in three binary logistic regression models (Table 2).

Two-step binary logistic regression analysis

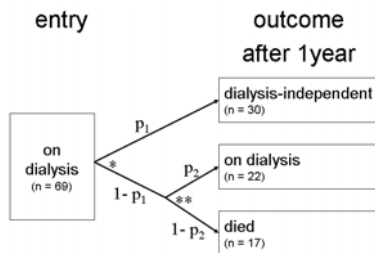
Type of adjunctive treatment, the percentage of normal glomeruli, the extent of tubular atrophy, the percentage of glomerulosclerosis, and the presence of arteriosclerosis were predictive in at least one of the three models differentiating between two outcomes (Table 2). On the basis of their predictive value, these

Table 2. Binary logistic regression models differentiating between two outcomes

Compared outcomes	Models	Variables	P	% correct	r ²	Exp β	95% CI of Exp β
Dialysis-independency (0) versus dialysis (1)	y = -1.3 - 2.5 x arm + 2.8 x tubular atrophy - 0.09 x normal glomeruli	Arm	0.008	77.8%	0.531	0.08	0.01 to 0.52
		Tubular atrophy	0.005			17.2	2.4 to 122.7
		Normal glomeruli	0.025			0.91	0.84 to 0.99
		Constant	0.189			0.27	
Dialysis (0) versus death (1)	y = 0.18 + 1.4 x arm - 0.04 x glomerulosclerosis	Arm	0.056	66.7%	0.256	4.1	0.97 to 17.4
		Glomerulosclerosis	0.061			0.03	0.001 to 1.2
		Constant	0.783			1.2	
Dialysis-independency (0) versus death (1)	y = -1.4 + 1.5 x arteriosclerosis	Arteriosclerosis	0.042	63.4%	0.147	4.7	1.1 to 20.5
		Constant	0.032			0.25	

The chance of a certain outcome can be calculated by the formula: $p = \text{Exp}(y) / [1 + \text{Exp}(y)]$. For treatment arm, IVMeP = 0, PE = 1. Tubular atrophy was scored as - / + / ++ and arteriosclerosis as - / +. Glomerulosclerosis and normal glomeruli are continuous parameters and expressed as the percentage of total number of glomeruli. Odds ratios are expressed as exponent β (Exp β); the 95% confidence intervals (95% CI) are also listed.

parameters were selected to be used in the two-step binary logistic regression analysis (Figure 1). This analysis was performed to design a prediction model. Values for sensitivity and predictive values of the two-step binary logistic regression analysis are given in Table 3.

**Figure 1.** Two-step binary logistic regression model.

The chance of becoming dialysis-independent is p_1 , the chance of being on dialysis is $(1 - p_1) \times p_2$, and the chance of dying is $(1 - p_1) \times (1 - p_2)$. * model 1: recovery (1) versus non-recovery (0) = $0.2 + 1.1 \times \text{limb [IVMeP=0, PE=1]} + 0.02 \times \text{normal glomeruli} - 0.01 \times \text{glomerulosclerosis} - 0.2 \times \text{tubular atrophy} - 1.4 \times \text{arteriosclerosis}$. ** model 2: death (1) versus dialysis (0) = $0.2 + 2.4 \times \text{limb} + 0.04 \times \text{normal glomeruli} - 0.03 \times \text{glomerulosclerosis} - 2.3 \times \text{tubular atrophy} + 1.8 \times \text{arteriosclerosis}$. In these equations, limb and arteriosclerosis are dichotomous variables, tubular atrophy is categorical (- / + / ++), and normal glomeruli and glomerulosclerosis are continuous variables (0-100%).

Table 3. Classification table of the two-step logistic regression model

		Predicted			total*	predicted/observed (sensitivity)
		dialysis-independent	on dialysis	dead		
Observed	dialysis-independent	13	4	7	24	54.2%
	on dialysis	4	14	3	21	66.7%
	dead	5	4	8	17	47.1%
	total	22	22	18	62	56.5%
observed/predicted (predictive value)		59.1%	63.6%	44.4%		

* Seven patients were unclassifiable for arteriosclerosis due to the absence of arteries in their biopsies.

Worst- and best-case scenarios according to the two-step binary logistic regression analysis

A patient with the lowest chance on dialysis independency and the highest chance on dialysis dependency would have the maximum of unfavorable factors within these study observations: intravenous methyl prednisolone as adjunctive treatment, 0% normal glomeruli, 88% glomerulosclerosis, severe tubular

atrophy, and arteriosclerosis. This patient has a chance of 6% of recovery, a 93% chance of dialysis dependency, and 1% chance of death.

A patient with the highest chance of dialysis independency and the lowest of dialysis dependency would have the minimum of unfavorable factors within these study observations: plasma exchange as adjunctive treatment, 89% normal glomeruli, no glomerulosclerosis, no tubular atrophy, and no arteriosclerosis. This patient has a 94% chance of recovery, a 0% chance of dialysis dependency, and a 6% chance of death.

Chances of dying

In this study, 17 patients died within the first year of follow-up. Two deaths were disease related, two patients died of vascular causes (myocardial infarction and gastrointestinal bleeding), one patient died of respiratory failure, and two patients died of unknown causes. Ten deaths were clearly therapy related; these were the result of infections, such as pneumocystis carinii pneumoniae and cytomegalovirus. Of the 10 patients who died of therapy-related causes, 7 came from the plasma exchange group (7/35, 20%) and 3 came from the intravenous methyl prednisolone group (3/34, 8.8%). Differences between the two groups were not statistically significant, as determined by the Fisher's exact test ($P = 0.306$).

From these analyses it became clear that the clinical and histological parameters studied could not distinguish very well between death, irrespective of the cause, and the other outcomes (i.e., dialysis dependency and independency; data not shown). This observation was confirmed by logistic regression analysis in which there were no predictive parameters for death or for therapy-related death (data not shown).

The chance of recovery can be calculated by using the logistic regression model of dialysis dependency versus dialysis independency at one year (Table 2), also taking into account the outcome of death. Analysis of the predictive values of the binary logistic regression model that differentiate best between dialysis dependency and independency after 12 months shows predictive values are reasonably high, namely: 80.0% for dialysis independency and 72.7% for dialysis dependency (data not shown).

A total of 17 of 69 patients died, resulting in a 25% chance of dying in this patient group. Considering the chances of dying in each treatment limb, the point at which the chance of dialysis independency is lower than the chance of dying can be determined from the number of normal glomeruli in combination

Table 4. Points at which the chance of dying from therapy exceeds the chance of recovery

Adjunctive treatment	Tubular atrophy	Normal glomeruli
iv methyl prednisolone	no	<0%
iv methyl prednisolone	moderate	<0%
iv methyl prednisolone	severe	18,1%
plasma exchange	no	<0%
plasma exchange	moderate	<0%
plasma exchange	severe	2.1%

When the % of normal glomeruli is less than the no. in the column, the chance of dying from therapy exceeds the chance of becoming dialysis-independent.

with the severity of tubular atrophy. This relationship is illustrated in Table 4, which shows that in patients treated with intravenous methyl prednisolone, the chance of dying from therapy is higher than the chance of dialysis independency in the case of severe tubular atrophy and less than 18% normal glomeruli. For patients on plasma exchange, the chance of dying from therapy is higher than the chance of dialysis independency in the case of severe tubular atrophy and less than 2% of normal glomeruli (Figure 2).

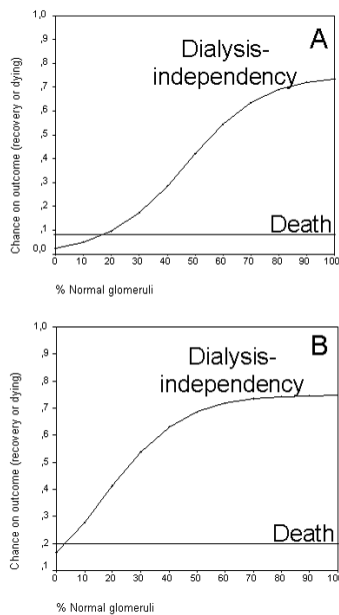


Figure 2. Chances of therapy-related death and dialysis-independency after one year related to the percentage of normal glomeruli in a diagnostic biopsy. Figures are shown for the patients that received intravenous methyl prednisolone as adjunctive treatment and showed severe tubular atrophy in their biopsies (A) and for the patients that received plasma exchange as adjunctive treatment and showed severe tubular atrophy in their biopsies (B). Left of the point where the lines cross, the chance of dialysis-independency drops below the chance of therapy-related death. For the patients with IVMeP this point is at 18% of normal glomeruli, while for the patients on PE this point is at 2% of normal glomeruli. IVMeP is intravenous methyl prednisolone, PE is plasma exchange.

Time from disease onset to death

Figure 3 shows data for all patients in this study who died within 1 year after disease onset, including the time-point at which they died and the cause of death. A pattern emerged that distinguished between therapy-related deaths and deaths attributable to other causes. All the patients who died from causes other than therapy-related causes ($n = 7$) did so within 3 months after diagnosis with a mean of 1.5 months, with vascular causes being responsible for the first two deaths. In contrast, all patients who died after 3 months died from therapy-related causes, with a mean from diagnosis to death of 5.6 months.

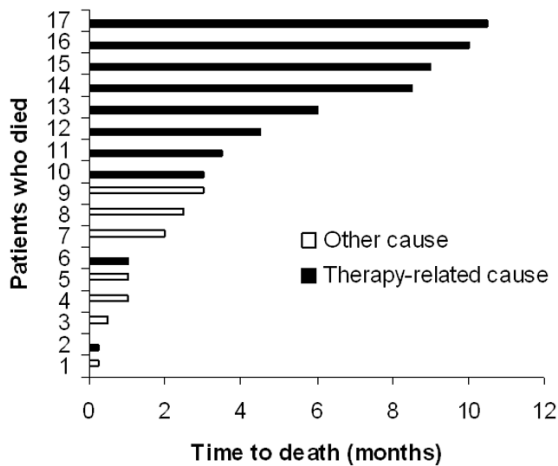


Figure 3. Causes of death divided by therapy-related causes and other causes.

Discussion

ANCA-associated glomerulonephritis is a rare entity. Patients affected by this disease who present with acute renal failure requiring dialysis are even rarer. In this prospective study, clinical and histological determinants of outcome in patients with dialysis-dependent ANCA-associated vasculitis at diagnosis were identified. In this patient group, the outcome after one year was as follows: 43% were dialysis independent, 32% were dialysis dependent, and 25% had died. Based on a two-step binary logistic regression analysis, estimated chances of recovery after one year in this patient group appeared to vary widely. This variability in outcome was mainly determined by: type of adjunctive treatment, percentage of normal glomeruli and glomerulosclerosis, the extent of tubular atrophy, and the presence of arteriosclerosis.

Models resulting from a two-step binary logistic regression analysis provided insight into the chances an individual patient has on becoming dialysis dependent or independent, or dying, within 1 year after diagnosis. The models

also gave insight into which histological and clinical variables predict outcome. Chronic lesions, in both the glomerular and the interstitial compartments, showed an inverse relationship with recovery. Glomerulosclerosis and arteriosclerosis also correlated with dialysis dependency at 1 year: this is a specific feature of patients with ANCA-associated glomerulonephritis who are dialysis dependent at diagnosis, as these parameters did not play a role in a previous analysis ²¹. Apparently, when patients are diagnosed with ANCA-associated vasculitis and are dialysis dependent, pre-existing vascular lesions have a high impact on renal outcome. This could be explained by the irreversibility of glomerulosclerosis and arteriosclerosis despite therapy. Type of adjunctive therapy was shown to be a predictor of dialysis independency at 12 months with plasma exchange as the adjunctive treatment of choice.

Outweighing the benefits against the hazards of treatment and making subsequent decisions on the basis of clinical information is a difficult task for the physician. This study shows that histopathological lesions may be of help in this decision-making process. The point at which the chance of therapy-related death became higher than the chance of dialysis independency could be calculated by taking into account the type of adjunctive treatment, the degree of tubular atrophy, and the number of normal glomeruli. However, when evaluating the percentages of normal glomeruli, the total number of glomeruli in a biopsy is of utmost importance. If tubular atrophy was severe and patients were treated with intravenous methyl prednisolone as adjunctive treatment, and they had less than 18% normal glomeruli, the chance of therapy-related death exceeded the chance of renal recovery. For those patients with severe tubular atrophy, treated with plasma exchange, if they had less than 2% normal glomeruli, their chance of therapy-related death would exceed their chance of renal recovery. Since the total number of glomeruli in the biopsies varied between 2 and 49, 2% normal glomeruli is negligibly small. If tubular atrophy was absent or moderate, the chance of renal recovery exceeded the chance of therapy-related death. From these data, the important conclusion can be drawn that even in patients who showed an ominous histological picture in their biopsies at diagnosis, the chance of renal recovery almost always exceeded the chance of therapy-related death if the patient was treated with plasma exchange as adjunctive therapy.

In an examination of the causes of death within the 12 months of the study, a subdivision emerges for the first 3 months of the disease and the period after 3 months. In the first 3-month period, death most often resulted from causes that

were not therapy related, such as the disease itself and vascular factors. Between 3 and 12 months, death was exclusively caused by therapy. Considering earlier reports that the addition of plasma exchange and intravenous methyl prednisolone facilitates the improvement of renal function within the first 3 months after disease onset²⁹⁻³¹, it is most striking that death due to therapy almost exclusively occurs in the period after 3 months. This phenomenon may be ascribed to the cumulative dose of immunosuppressive treatment, when combining standard treatment with adjunctive treatment, according to the regimen used in this study. Moreover, this finding suggests that improved and safer treatment regimens are required for patients with ANCA-associated glomerulonephritis and dialysis dependency at diagnosis.

For this study, the treatment regimen with aggressive adjunctive treatment was aimed at restoring renal function within a short period of time and therefore, follow-up was limited to 12 months. Results indeed showed that if recovery took place, the patient's renal function stabilized within 3 months, which justified the duration of follow-up within the scope of this study. Although this is the largest-to-date study of a homogeneously treated cohort of dialysis dependent ANCA-associated vasculitis patients, the number of patients could be expanded for firmer predictions. The sample size of this patient group may appear relatively limited, but can be explained by the very low incidence of this particular disease. Only through a collaborative study in which many European centers have joined efforts to contribute patient data, we were able to gather this group which is extremely homogeneous in terms of clinical status (i.e. dialysis dependency at diagnosis) and treatment. The number of patients is also the reason a two-step binary logistic regression analysis was performed instead of a multinomial logistic regression analysis; they are essentially the same, but using the two-step analysis provided more insight into the process of how predictive models are constructed. The predictive value of the two-step binary logistic regression model is somewhat limited, but it illustrates the factors associated with and that are predictors of certain outcomes. An important cause of this limited predictive value is probably the inability to predict death. Because death can be considered as a given chance, factors were distinguished that could differentiate between dialysis dependency and dialysis independency. Because many patients die as a result of adverse effects of therapy, there should be careful consideration about exposing them to an aggressive immunosuppressive treatment in case of renal failure. If it were possible to predict which patients would not recover from renal insufficiency,

treatment in those patients could target suppressing disease activity in other involved organs and the achievement and maintenance of remission. Bearing in mind that most patients are affected not only by renal involvement but also by systemic disease, stopping immunosuppressive treatment completely is usually not an option.

Recently, we published a paper in which predictive parameters of outcome were investigated in a group of ANCA-associated vasculitis patients presenting with acute deterioration of renal function ²¹. In the present study, we have focused on patients who require dialysis at presentation, identifying factors that are important in determining renal function recovery and associated these factors with therapy-related deaths. Moreover, the current study provides insight into factors that are important in treatment decision-making. In conclusion, in patients with dialysis-dependent, ANCA-associated vasculitis, the chances of recovery differ depending on the type of adjunctive treatment, the percentage of normal glomeruli and glomerulosclerosis, the extent of tubular atrophy, and the presence of arteriosclerosis. Even with an ominous biopsy at diagnosis in combination with dialysis dependency, the chance of renal recovery exceeds the chance of therapy-related death if the patient is treated with plasma exchange as adjunctive treatment. Therapy-related death usually occurs between 3 and 12 months after diagnosis. Prevention of therapy-related death requires safer treatment regimens for patients with ANCA-associated glomerulonephritis who are already dialysis dependent at diagnosis.

Acknowledgements

Elements of this study were presented at the American Society of Nephrology 2005 Annual Meeting in Philadelphia, PA (*J Am Soc Nephrol* 16:69A, 2005).

This trial was designed and launched as part of the European Community Systemic Vasculitis Trial project (Contract nos. BMH1-CT93-1078 and CIPD-CT94-0307) and finished as part of the Associated Vasculitis European Randomised Trial project (Contract nos. BMH4-CT97-2328 and IC20-CT97-0019) funded by the European Union. We thank the following: NJD Nagelkerke, J Hermans and JC van Houwelingen, Leiden, Netherlands; P Landais, Paris, France; J Thorogood, London, UK (statistical advice); H Talbot, Edinburgh, UK (software design); F Compton, London, UK (data management); L Jayne, London, UK (trial administration).

Participating clinical physicians:

D Blockmans, *Universitair Ziekenhuis, Leuven, Belgium*. M Dhaene, J Sennesael, *Academic Hospital of the Free University, Bruxelles, Belgium*. A Wiik, *Statens Serum Institute, Copenhagen, Denmark*. A Ekstrand, C Grönholm-Riska, *University of Helsinki, Finland*. P Lesavre, *Hôpital Necker, Paris, France*. P Bataille, *Centre Hospitalier General,*

Boulogne sur Mer, **France**. L Guillevin, *Hôpital Avicenne, Bobigny, France*. P Vanhille, *Centre Hospitalier, Valenciennes, France*. O Hergesell, K Andrassy, *Heidelberg University Hospital, Germany*. E Reinhold-Keller, *Rheumaklinik Bad Bramstedt, Germany*. C Specker, M Schneider, *Heinrich-Heine University, Düsseldorf, Germany*. M Haubitz, *Medical School Hannover, Germany*. F van der Woude, *Klinikum Mannheim, Germany*. H Rupprecht, S Weidner, *Klinikum Nürnberg, Germany*. A Natusch, *Klinikum Buch, Berlin, Germany*. M Abuzakouk, *St James's Hospital, Dublin, Ireland*. A Sinico, *Ospedale San Carlo Borromeo, Milan, Italy*. G Poissetti, *Ospedale Civile, Piacenza, Italy*. J Dadonienė, *University of Vilnius, Lithuania*. C Verburch, *Leiden University Medical Center, The Netherlands*. E Mirapeix, *Hospital Clinic I Provincial, Barcelona, Spain*. R Poveda, *Hospital Princes d'Espana, Llobregat, Spain*. M Heimburger, *Huddinge University Hospital, Sweden*. E Theander, K Westman, M Segelmark, *University Hospital of Malmö, Sweden*. Z Heigl, I Lundberg, E Svenungsson, *Karolinska Sjukhuset, Sweden*. J Gibson, *Windygates Hospital, Fife, UK*. D Adu, C Savage, and L Harper, *Queen Elizabeth II Hospital, Birmingham, UK*. P Mathieson and C Tomson, *Southmead Hospital, Bristol, UK*. J Freehally, *University Hospital, Leicester, UK*. Aine Burns, *Royal Free Hospital, London, UK*. D Oliveira, *St George's Hospital, London, UK*. R Luqmani, *John Radcliffe Hospital, Oxford, UK*. M Rogerson and J Stevens, *Southampton Hospital, UK*. A Williams, *Morrison Hospital, Swansea, UK*.

Pathologists who provided biopsy material:

B van Damme, *University Hospital Leuven, Belgium*. M Depierreux, C Bourgain, *Academic Hospital of the Free University, Bruxelles, Belgium*. T Törnroth, *University of Helsinki, Finland*. AC Feller, *University of Luebeck, Germany*. E Gaffney, *Saint James's Hospital, Dublin, Ireland*. R Tardanico, *Ospedale Civile, Brescia, Italy*. R Consalonieri, *Ospedale Maggiore CA Granda, Milan, Italy*. G Garibotto, *ISUL, Genova, Italy*. ATMG Tiebosch, *Academic Hospital, Groningen, The Netherlands*. CD Kooijman, *Eemland Hospital, Amersfoort, The Netherlands*. M Sole Arques, *Hospital Clinic I Provincial de Barcelona, Spain*. F Algaba, *Puigvert, Barcelona, Spain*. M Carrera, *Hospital Princes d'Espana, Llobregat, Spain*. M Carreras, *Hospital de Bellvitge, Barcelona, Spain*. M Vaquero Perez, *Hospital Universitari Germans Trias I Pujol, Badalona, Spain*. L Bernardo, *Hospital Dr. Josep Trueta, Girona, Spain*. A Wernersson, *Huddinge University Hospital, Sweden*. B Sundelin, *Karolinska Hospital, Stockholm, Sweden*. M Simanaitis, B Veress, *University Hospital MAS, Malmö, Sweden*. P Alm, *University Hospital of Lund, Sweden*. AJ Howie, *University Hospital Birmingham, UK*. D Griffiths, D Kamel, *Southmead Hospital, Bristol, UK*. S Fleming, *University Department of Pathology, Edinburgh, UK*. PN Furness, *Leicester Area Histopathology Service, UK*. HT Cook, *Hammersmith Hospital, London, UK*. W Landells, *Saint Helier Hospital, London, UK*. I Roberts, *John Radcliffe Hospital, Oxford, UK*. AP Griffith, *Morrison Hospital, Swansea, UK*.

References

1. Pettersson EE, Sundelin B, Heigl Z: Incidence and outcome of pauci-immune necrotizing and crescentic glomerulonephritis in adults. *Clin Nephrol* 43:141-149, 1995
2. Bindi P, Gilson B, Aymard B, Brillet G, Birembaut P, Joly D: Extracapillary and necrotizing glomerulonephritis without immunoglobulin deposits: clinical presentation, prognostic factors and response to treatment. Apropos of 42 cases. *Nephrologie* 14:95-100, 1993
3. Slot MC, Tervaert JW, Franssen CF, Stegeman CA: Renal survival and prognostic factors in patients with PR3-ANCA associated vasculitis with renal involvement. *Kidney Int* 63:670-677, 2003
4. Little MA, Nazar L, Farrington K: Outcome in glomerulonephritis due to systemic small vessel vasculitis: effect of functional status and non-vasculitic co-morbidity. *Nephrol Dial Transplant* 19:356-364, 2004
5. Weidner S, Geuss S, Hafezi-Rachti S, Wonka A, Rupperecht HD: ANCA-associated vasculitis with renal involvement: an outcome analysis. *Nephrol Dial Transplant* 19:1403-1411, 2004
6. Booth AD, Almond MK, Burns A, Ellis P, Gaskin G, Neild GH, Plaisance M, Pusey CD, Jayne DR: Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. *Am J Kidney Dis* 41:776-784, 2003
7. Kaplan-Pavlovic S, Cerk K, Kveder R, Lindic J, Vizjak A: Clinical prognostic factors of renal outcome in anti-neutrophil cytoplasmic autoantibody (ANCA)-associated glomerulonephritis in elderly patients. *Nephrol Dial Transplant* 18 Suppl 5:v5-v7, 2003
8. Falk RJ, Jennette JC: ANCA small-vessel vasculitis. *J Am Soc Nephrol* 8:314-322, 1997
9. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, Rottem M, Fauci AS: Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 116:488-498, 1992
10. Andrassy K, Erb A, Koderisch J, Waldherr R, Ritz E: Wegener's granulomatosis with renal involvement: patient survival and correlations between initial renal function, renal histology, therapy and renal outcome. *Clin Nephrol* 35:139-147, 1991

11. Gayraud M, Guillevin L, le Toumelin P, Cohen P, Lhote F, Casassus P, Jarrousse B: Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. *Arthritis Rheum* 44:666-675, 2001
12. Nachman PH, Hogan SL, Jennette JC, Falk RJ: Treatment response and relapse in antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol* 7:33-39, 1996
13. Glasscock RJ: Intensive plasma exchange in crescentic glomerulonephritis: help or no help? *Am J Kidney Dis* 20:270-275, 1992
14. Guillevin L, Lhote F: Treatment of polyarteritis nodosa and microscopic polyangiitis. *Arthritis Rheum* 41:2100-2105, 1998
15. Aasarod K, Bostad L, Hammerstrom J, Jorstad S, Iversen BM: Wegener's granulomatosis: inflammatory cells and markers of repair and fibrosis in renal biopsies—a clinicopathological study. *Scand J Urol Nephrol* 35:401-410, 2001
16. McLaughlin K, Jerimiah P, Fox JG, Mactier RA, Simpson K, Boulton-Jones JM: Has the prognosis for patients with pauci-immune necrotizing glomerulonephritis improved? *Nephrol Dial Transplant* 13:1696-1701, 1998
17. Neumann I, Kain R, Regele H, Soleiman A, Kandutsch S, Meisl FT: Histological and clinical predictors of early and late renal outcome in ANCA-associated vasculitis. *Nephrol Dial Transplant* 20:96-104, 2005
18. Vergunst CE, van Gurp E, Hagen EC, van Houwelingen HC, Hauer HA, Noel LH, Waldherr R, Ferrario F, van der Woude FJ, Bruijn JA, Bajema IM: An index for renal outcome in ANCA-associated glomerulonephritis. *Am J Kidney Dis* 41:532-538, 2003
19. Fauci AS, Haynes B, Katz P: The spectrum of vasculitis: clinical, pathologic, immunologic and therapeutic considerations. *Ann Intern Med* 89:660-676, 1978
20. Savage CO, Harper L, Adu D: Primary systemic vasculitis. *Lancet* 349:553-558, 1997
21. de Lind van Wijngaarden RA, Hauer HA, Wolterbeek R, Jayne DR, Gaskin G, Rasmussen N, Noel LH, Ferrario F, Waldherr R, Hagen EC, Bruijn JA, Bajema IM: Clinical and histologic determinants of renal outcome in ANCA-associated vasculitis: A prospective analysis of 100 patients with severe renal involvement. *J Am Soc Nephrol* 17:2264-2274, 2006

22. Jayne DR, Rasmussen N: Treatment of antineutrophil cytoplasm autoantibody-associated systemic vasculitis: initiatives of the European Community Systemic Vasculitis Clinical Trials Study Group. *Mayo Clin Proc* 72:737-747, 1997
23. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, Hagen EC, Hoffman GS, Hunder GG, Kallenberg CG: Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 37:187-192, 1994
24. Hagen EC, Daha MR, Hermans J, Andrassy K, Csernok E, Gaskin G, Lesavre P, Ludemann J, Rasmussen N, Sinico RA, Wiik A, van der Woude FJ: Diagnostic value of standardized assays for anti-neutrophil cytoplasmic antibodies in idiopathic systemic vasculitis. EC/BCR Project for ANCA Assay Standardization. *Kidney Int* 53:743-753, 1998
25. Hauer HA, Bajema IM, van Houwelingen HC, Ferrario F, Noel LH, Waldherr R, Jayne DR, Rasmussen N, Bruijn JA, Hagen EC: Determinants of outcome in ANCA-associated glomerulonephritis: a prospective clinico-histopathological analysis of 96 patients. *Kidney Int* 62:1732-1742, 2002
26. Hogan SL, Nachman PH, Wilkman AS, Jennette JC, Falk RJ: Prognostic markers in patients with antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol* 7:23-32, 1996
27. Bajema IM, Hagen EC, Hermans J, Noel LH, Waldherr R, Ferrario F, van der Woude FJ, Bruijn JA: Kidney biopsy as a predictor for renal outcome in ANCA-associated necrotizing glomerulonephritis. *Kidney Int* 56:1751-1758, 1999
28. Bajema IM, Hagen EC, Hansen BE, Hermans J, Noel LH, Waldherr R, Ferrario F, van der Woude FJ, Bruijn JA: The renal histopathology in systemic vasculitis: an international survey study of inter- and intra-observer agreement. *Nephrol Dial Transplant* 11:1989-1995, 1996
29. Pusey CD, Rees AJ, Evans DJ, Peters DK, Lockwood CM: Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. *Kidney Int* 40:757-763, 1991
30. Bruns FJ, Adler S, Fraley DS, Segel DP: Long-term follow-up of aggressively treated idiopathic rapidly progressive glomerulonephritis. *Am J Med* 86:400-406, 1989
31. Bolton WK, Sturgill BC: Methylprednisolone therapy for acute crescentic rapidly progressive glomerulonephritis. *Am J Nephrol* 9:368-375, 1989

